Vasoactive responses of a human cystic artery: adrenoceptor characterization

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1 The pharmacology of various agonists and antagonists was studied in the human isolated cystic artery.

2 The estimated pA_2 s for the α_1 -adrenoceptor antagonist prazosin against the α -adrenoceptor agonists phenylephrine, α -methylnoradrenaline and noradrenaline were not significantly different. Similar results were seen for estimated pA_2 s of the α_2 -adrenoceptor antagonist yohimbine against these same agonists. Equivalent responses to exogenous noradrenaline and to transmural electrical stimulation were blocked to the same degree by an antagonist with α_1 -adrenoceptor blocking properties (prazosin). Responses to transmural electrical stimulation, however, tended to be more resistant than equivalent responses to exogenous noradrenaline to blockade by antagonists with α_2 -adrenoceptor blocking properties (phentolamine, yohimbine).

3 Relaxation to isoprenaline was observed in partially contracted arterial strips using isoprenaline concentrations of up to $10^{-6}M$, but cumulative addition of higher concentrations of isoprenaline sometimes then evoked a contraction from the relaxation nadir. The relaxation effect of isoprenaline was antagonized by propranolol ($10^{-5}M$).

4 These findings suggest the human cystic artery has almost exclusively α_1 -adrenoceptors postjunctionally, although prejunctional α_2 -adrenoceptors may be present; and, it also has some postjunctional β -adrenoceptors which mediate relaxation.

Keywords human artery α -adrenoceptors β -adrenoceptors

Introduction

The cystic artery is a muscular downstream branch of the hepatic artery and is readily available to us for *in vitro* studies. We have found responsiveness to some vasoactive agents is altered in mild hypertensives (Wyse, 1984). Vasoactive responses of this artery have been incompletely characterized (Wyse, 1981). Species differences of *in vitro* vascular responses and heterogeneity of such responses among different vessels of the same species (Toda, 1985; Vanhoutte & Shepherd, 1985) preclude generalizations from other work concerning vasoactive responses of this artery. In order to study altered responsiveness of cystic

artery in hypertension in more detail, it was first necessary to make an assessment of adrenoceptors present in the artery. Accordingly, the present experiments were undertaken to characterize more completely adrenoceptor responses of human cystic artery.

Methods

Subjects

Patients admitted to the Foothills Hospital for elective cholecystectomy for lithiasis were

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approached and informed consent was obtained. A patient history was elicited via a written questionnaire and subjects were excluded when this revealed any current medical condition other than cholelithiasis. Patients taking any chronic medication with cardiovascular effects were also excluded. The following laboratory tests were performed: serum K^+ , serum creatinine and a urinalysis. Patients were excluded when there was any abnormality in these laboratory investigations. Finally, the pathologic report on the gallbladder was examined *post hoc* and patients were excluded if any abnormality was noted in addition to uncomplicated lithiasis. Three lying and standing blood pressures were measured on the first hospital day and averaged. Patients with an average diastolic blood pressure of greater than 95 mm Hg were excluded from the present study.

Arterial strips

Immediately upon removal of the gallbladder, the extramural artery was removed and placed in modified Krebs-Henseleit bicarbonate solution (NaCl, 115.3, KCl, 4.6, $CaCl_2$, 1.8, $MgSO_4$, 1.1, $NaHCO_3$, 22.1, glucose, 7.8, ascorbic acid, 0.11, and disodium EDTA, 0.027 mM) and gassed with 5% CO_2 in oxygen. It was transported to the laboratory where excess fat and connective tissue were trimmed away taking care not to damage the outer *tunica adventitia* or inner *tunica intima* (endothelium). Helical strips were cut under a dissecting microscope at an angle of approximately 60° to the long axis of the vessel. Strips of artery were suspended between two parallel platinum wire electrodes in a 10 ml muscle bath containing Krebs-Henseleit solution at $36 \pm 1^\circ C$ and gassed with 5% CO_2 in oxygen. The tension required to produce optimum resting length was determined for each strip as previously described (Wyse, 1980) and applied to the strip. Tension changes were recorded isometrically. One to three arterial strips were obtained from each subject.

Electrical stimulation

Transmural electrical stimulation was usually started immediately after the length-tension determination. The techniques for electrical stimulation of postganglionic adrenergic nerve endings in the vessel wall have been described in detail elsewhere (Kassay-Farkas & Wyse, 1986). In the present experiments biphasic rectilinear pulses with a total pulse width of 1.6 ms were used. Stimuli were administered from two Grass model S48 stimulators via two Grass model SIU5

stimulus isolation units. The output waveform was then amplified by an Intensil amplifier (Model ICH 5301 KA). The voltages between the anode and cathode in the bath fluid and across a 1 ohm resistance connected in series were monitored on a Tektronix Type 205 oscilloscope. The current delivered to the bath was individually amplified to 1.0 A for each electrode. After a 30 s train of stimulation at one frequency followed by 90 s rest, the next frequency was tested without changing the bath solution. Frequencies tested were 2, 4, 8, 12 and 16 Hz. These settings have previously been demonstrated to the supramaximal and they do not accelerate oxidation of noradrenaline in the bath fluid (Kassay-Farkas & Wyse, 1986).

Concentration-response curves

Up to four different agonists were tested in any one arterial strip. Noradrenaline was always the last agonist tested but otherwise the order of testing was random. Relaxation produced by isoprenaline was evaluated by adding this agonist while the strip was partially contracted with 5-hydroxytryptamine. All concentration-response curves were done in a cumulative fashion and half to full log increments in final bath concentration were used. The following ranges of concentration (M) were studied: 5-hydroxytryptamine 10^{-8} to 3×10^{-5} ; noradrenaline 10^{-9} to 10^{-3} ; α -methylnoradrenaline 3×10^{-8} to 10^{-4} ; phenylephrine 3×10^{-6} to 10^{-3} ; and, isoprenaline 10^{-7} to 10^{-5} . For 5-hydroxytryptamine and isoprenaline the concentrations used only partially defined the concentration-response relationship.

Adrenoceptor antagonists

Adrenoceptor antagonists were added to the bath fluid and allowed to equilibrate for at least 15 min prior to repeat electrical or agonist stimulation. Concentrations (M) of antagonists used in the present study were as follows: prazosin 2.4×10^{-8} to 7.2×10^{-7} ; yohimbine 2.6×10^{-7} to 3×10^{-6} ; phentolamine 8.1×10^{-7} and 2.7×10^{-6} ; and, propranolol 10^{-5} .

Data

Continuous data are presented as the mean $\pm$ 1 s.e. mean. No patient contributed more than one arterial strip to each experiment, i.e. n is the number of subjects in each case. A calculation of the EC_{50} s for noradrenaline, α -methylnoradrenaline or phenylephrine was made by linear regression of probits (Tallarida & Murray, 1981) before and after treatment with antagonist and

the pA_{2s} for each antagonist were estimated using a single antagonist concentration (Horwitz *et al.*, 1974). Data from the same strip were compared using the paired *t*-test. Data from different strips were compared by unpaired *t*-test for a single comparison or one-way analysis of variance and Tukey's test for more than one comparison. The Null Hypothesis was rejected when P was < 0.05 . Statistical analysis used programs in the Statistical Package for Social Sciences (Nie *et al.*, 1975).

Drugs

The following drugs were supplied by Sigma Chemical company, St Louis MO, USA: noradrenaline bitartrate, isoprenaline bitartrate, 5-hydroxytryptamine creatinine sulfate complex, yohimbine hydrochloride, and propranolol hydrochloride. Other drugs and their suppliers were: phentolamine mesylate by Ciba-Geigy Canada Ltd; and prazosin hydrochloride by Pfizer Canada Ltd. Yohimbine and prazosin were dissolved in dilute ethanol solutions (final bath concentrations of ethanol 2 and 5×10^{-4} mol l^{-1}) but all other drugs were dissolved in water. Final bath concentrations are expressed as mol l^{-1} .

Results

Subjects

For the experiments described in the present study 75 female and 32 male subjects who ranged in age from 17 to 68 years with a mean age of 41 ± 1 years were used. The average systolic, diastolic and mean blood pressures of these subjects were 118 ± 1 , 76 ± 1 and 90 ± 1 mm Hg, respectively. A total of 205 arterial strips were studied and the mean noradrenaline induced maximum tension response was 2.74 ± 0.17 g.

Responses to α -adrenoceptor agonists and effects of antagonists

The effects of α -adrenoceptor blocking agents are presented in Figures 1, 2, 3 and 4. A sample pen tracing showing the blocking effect of prazosin (10^{-7} M) against noradrenaline is provided in Figure 1. Responses of untreated control tissues tended to deteriorate slightly during longer experiments as can be seen in Figure 4. This was particularly evident in the first portion (responses $< 30\%$ of maximum) of the noradrenaline concentration-response curve and because the magnitude of responses to transmural electrical stimulation falls within this range, interpretation of these particular responses is more complicated (see below). This problem would also complicate use of multiple antagonist concentrations to determine pA_2 by Schild plots. The concentration of ethanol used as a solvent for antagonists did not augment time-dependent deterioration of responses (*cf* prazosin and yohimbine controls to phentolamine control in Figure 4) and there were no other demonstrable effects of the ethanol concentrations used for solvent purposes in this study.

Clonidine did not elicit a contraction in this artery in concentrations up to 10^{-3} M. However, α -methylnoradrenaline and phenylephrine both elicited contractions with maximal responses similar to those seen with noradrenaline (Figure 2), albeit their concentration-response curves were further to the right (sensitivity = phenylephrine $< \alpha$ -methylnoradrenaline $< \text{noradrenaline}$). Estimated pA_{2s} (see **Methods**) for prazosin *vs* noradrenaline, α -methylnoradrenaline and phenylephrine were 9.3 ± 0.3 , 9.3 ± 0.4 and 8.8 ± 0.3 , respectively and were not significantly different from one another (Panel a, Figure 2). Estimated pA_{2s} for yohimbine *vs* noradrenaline, α -methylnoradrenaline and phenylephrine were 5.9 ± 0.2 , 6.3 ± 0.3 and 6.6 ± 0.5 , respectively and also were not significantly different from one another (Panel b, Figure 2).

Figure 1 Sample pen tracing showing the effect of prazosin (10^{-7} M) on responses to noradrenaline.

Figure 2 Comparison of the effects of prazosin (10^{-7} M, Panel a) and yohimbine (3×10^{-6} M, Panel b) on responses to noradrenaline (NA, top panel) α -methylnoradrenaline (α Me NA, middle panel) and phenylephrine (PE, bottom panel). Vertical axes are responses expressed as a percent of the noradrenaline-induced maximum contraction prior to treatment. Open circles represent responses prior to treatment (baseline). Closed circles represent responses observed after treatment. Vertical lines are ± 1 s.e. mean, $n = 9$ to 11.

The ability of these two α -adrenoceptor blocking agents and the nonselective agent phentolamine to block responses to exogenous noradrenaline or 5-hydroxytryptamine and those due to amine released by electrical stimulation was assessed in a separate set of experiments. Prazosin, yohimbine and phentolamine all caused concentration-dependent parallel shifts in the concentration-response curve for noradrenaline without reduction of the maximum response (Panel a, Figure 3). Reduction of 5-hydroxytryptamine responses was only observed with prazosin and the higher concentration of phentolamine; yohimbine had no effect on responses to 5-hydroxytryptamine (Panel b, Figure 3). Prazosin blocked responses to exogenous noradrenaline and transmurial electrical stimulation

to the same degree, whereas responses to transmurial electrical stimulation were somewhat resistant to yohimbine and phentolamine and this is illustrated in Figure 4. Data in Figure 4 were obtained by matching a baseline (pretreatment) response to electrical stimulation to the baseline (pretreatment) response to exogenous noradrenaline in the same arterial strip which was closest in magnitude to the electrically-induced response. Recall that responses to electrical stimulation are a fraction of the noradrenaline maximum (10 to 20% in this instance). Note thus, the similarity in height of the open bars in each panel of Figure 4 which are these matched baseline or pretreatment responses. Responses after a period of time or after time and exposure to an α -adrenoceptor antagonist are illustrated

Figure 3 Comparison of the effects of prazosin (left panel), yohimbine (middle panel), and phentolamine (right panel) on responses to exogenous noradrenaline (NA, Panel a) and 5-hydroxytryptamine (5-HT, Panel b). In this figure data prior to treatment are not illustrated although the vertical axes are responses as a percent of the noradrenaline-induced maximum contraction prior to treatment (baseline). Solid triangles represent data after time or ethanol (solvent) alone. Solid squares are effects of: 2.4×10^{-8} M prazosin, 2.6×10^{-7} M yohimbine or 8.1×10^{-7} M phentolamine. Solid circles are time plus: 7.2×10^{-7} M prazosin, 3×10^{-6} M yohimbine or 2.7×10^{-6} M phentolamine. Vertical lines represent ± 1 s.e. mean, $n = 8$ to 12.

by the cross-hatched bars. In the case of time-dependent deterioration alone or with ethanol (control, all top panels) and the effects of prazosin (middle and bottom left panels), responses to noradrenaline and electrical stimulation fell in parallel. However, responses to electrical stimulation are resistant to blockade by yohimbine (central and lower middle panels) and the same trend is seen with phentolamine at the higher concentration (lower right panel) although this last difference did not achieve statistical significance.

Responses to a β -adrenoceptor agonist and effects of an antagonist

Isoprenaline induced a modest relaxation of arterial strips partially contracted by 5-hydroxytryptamine (left panel, Figure 5). The maximum relaxation observed was approximately 20% of the noradrenaline-induced maximum contraction. When the concentration of isoprenaline was

increased beyond 10^{-6} M, arterial strips often contracted again from the nadir of relaxation but these contractions never exceeded the original contraction. The relaxant effect of isoprenaline was significantly reduced by propranolol (10^{-5} M; right panel of Figure 5) but this concentration of propranolol did not cause total 'reversal' of isoprenaline responses to contraction rather than relaxation. This concentration of propranolol (10^{-5} M) had no effect on contractions elicited by exogenous noradrenaline (lower panel of Figure 6). In the upper right panel of Figure 6 the time-dependent deterioration of contractions elicited by transmural electrical stimulation again complicate interpretation and it cannot be ascertained if propranolol has any effect on responses to electrical stimulation in this experiment.

Discussion

The present results underscore the potential for errors when extrapolating results from other

Figure 4 Comparison of the ability of prazosin, yohimbine and phentolamine to block equivalent responses to exogenous and neurally-released noradrenaline (NA, see text for detailed description). Open bars are responses prior to treatment (baseline) and cross-hatched bars are responses after time alone (control, upper panels) or time plus α -adrenoceptor blockade (middle and lower panels). Vertical axes are responses as a % of the noradrenaline-induced maximum contraction at baseline. NA indicates responses to exogenous noradrenaline and TS those to transmurally electrical stimulation. Lower concentrations are: 2.4×10^{-8} M prazosin, 2.6×10^{-7} M yohimbine and 8.1×10^{-7} M phentolamine. Higher concentrations are: 7.2×10^{-7} M prazosin, 3×10^{-6} M yohimbine and 2.7×10^{-6} M phentolamine. Vertical lines on top of the bars indicate ± 1 s.e. mean * = $P < 0.05$, NA compared with TS, $n = 8$ to 12.

species and other vascular beds to interpretation of responses to vasoactive agents in a specific human artery.

α -adrenoceptor responses

There is now considerable evidence that α_2 -adrenoceptors are found postjunctionally in some arteries of certain species and can contribute to the contractile response to α -adrenoceptor agonists (see recent review of Matthews *et al.*, 1984). The present experiments suggest that

there is no significant number of postjunctional α_2 -adrenoceptors in the human cystic artery. No response could be elicited with the selective α_2 -adrenoceptor agonist, clonidine (Ruffolo, 1984). Although responses were observed with the α_2 -adrenoceptor agonist, α -methylnoradrenaline, the estimated pA_2 of the α_2 -adrenoceptor antagonist yohimbine against this agonist was the same as it was for the α_1 -adrenoceptor agonist phenylephrine and the mixed α -adrenoceptor agonist noradrenaline (Ruffolo, 1984). The concentrations of yohimbine necessary to

Figure 5 Concentration-response relationship for isoprenaline-induced relaxation in partially contracted arterial strips and effect of propranolol (10^{-5} M) on these responses. Vertical axes are % of the noradrenaline-induced (NA) maximum contraction prior to treatment (baseline, ○) for the purpose of standardized comparison. ● represent responses after time alone (left panel) or time plus propranolol (right panel). Vertical lines are ± 1 s.e. mean. * = $P < 0.05$ compared with baseline, $n = 10$.

observe an effect were also of a magnitude which has been found in other species and tissues to be greater than that which produces a selective α_2 -adrenoceptor blockade (Skarby *et al.*, 1983). Furthermore the estimated pA_{2S} for the selective α_1 -adrenoceptor antagonist prazosin (Ruffolo, 1984) were the same for all three α -adrenoceptor agonists used. Although the importance of selective inhibition of elimination pathways during determination of pA_2 (Kenakin & Beek, 1981) has been stressed, this was not done in the present study. Thus the pA_{2S} reported here may not be precise. However, relative to one another they should not be substantially different if inhibitors of uptake and β -adrenoceptors were present. Furthermore, the present data suggest that β -receptor inhibition may not substantially alter pA_2 determinations in view of their limited function in this artery. Unpublished results from this laboratory also indicate there is no capacity for nonneuronal uptake of noradrenaline in this artery and neuronal uptake in the 15 min required to complete a noradrenaline concentration-response curve is limited. Thus in spite of limitations, the estimates of pA_2 in the present study probably have validity.

There is, however, some weak evidence for the presence of prejunctional α_2 -adrenoceptors in the present experiments. A widely held viewpoint is that prejunctional α_2 -adrenoceptors, when activated, exert a negative feedback effect on

further neurotransmitter release (Westfall, 1984). If one accepts this hypothesis, it follows that in an artery where there are only postjunctional α_1 -adrenoceptors and few or no postjunctional α_2 -adrenoceptors (such as the cystic artery), a receptor antagonist with only α_1 -adrenoceptor blocking properties (such as prazosin) would have a greater effect on responses to neuronally-released noradrenaline (transmural electrical stimulation) than would agents with both α_1 - and α_2 -adrenoceptor blocking properties (such as phentolamine and high concentrations of yohimbine). This is precisely the effect which was observed in the present experiments.

We have previously observed inhibition of responses to 5-hydroxytryptamine by the α -adrenoceptor blocking agent phentolamine in this artery (Wyse, 1981). In the present study, only those α -adrenoceptor antagonists with α_1 -adrenoceptor blocking properties (prazosin and high concentrations of phentolamine) reduced responses to 5-hydroxytryptamine. This finding is in keeping with the hypothesis that 5-hydroxytryptamine acts partially through activation of postjunctional α -adrenoceptors and in human cystic artery these are all of the α_1 subtype. However, the interaction between 5-hydroxytryptamine and these antagonists is complex in man and in other species (Innes, 1962; Apperley *et al.*, 1980; Docherty & Hyland, 1986) and no experiments were included in the

Figure 6 Comparison of the effect of propranolol (10^{-5} M, right panels) on responses to transmural electrical stimulation (Hz, upper panels) and exogenous noradrenaline (NA, lower panels). Vertical axes are responses expressed as a % of the noradrenaline-induced maximum contraction prior to treatment (baseline). ○ represent these baseline responses. ● indicate responses after time alone (left panels) or time plus propranolol (right panels). Vertical lines indicate ± 1 s.e. mean * = $P < 0.05$ compared with baseline, $n = 10$.

present work to characterize the action of 5-hydroxytryptamine more completely in human cystic artery.

β -adrenoceptor responses

There is clear evidence in the present experiments for the presence of postjunctional β -adrenoceptors in the human cystic artery. Relaxation of partially contracted arterial strips was noted with the β -adrenoceptor agonist isoprenaline and these responses were antagonized by the non-selective β -adrenoceptor antagonist propranolol. The fact that higher concentrations of isoprenaline produced contractions is also in keeping with previous observations in other human blood vessels which suggest that isoprenaline is a weak α -adrenoceptor agonist in high concentrations (Coupar, 1970).

The present experiments cannot be used to

either support or deny the concept that there are presynaptic β -adrenoceptors which exert a positive feedback effect on neurotransmitter release in this artery as has been previously proposed for other arteries (Verbeuren *et al.*, 1983; Westfall, 1984). The tendency for deterioration in responses to transmural electrical stimulation noted in the present experiments prevents any comment on the effects of propranolol.

Conclusions

These findings suggest that the human cystic artery:

- has almost exclusively α_1 -adrenoceptors postjunctionally, although prejunctional α_2 -adrenoceptors which modulate neurotransmitter release (negative feedback) may be present.
- has postjunctional β -adrenoceptors which mediate relaxation.

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References

- Apperley, E., Feniuk, W., Humphrey, P. P. A., & Levy, G. P. (1980). Evidence for two types of excitatory receptor for 5-hydroxytryptamine in dog isolated vasculature. *Br. J. Pharmac.*, **68**, 215–224.
- Coupar, I. M. (1970). The effect of isoprenaline on adrenoceptors in human saphenous vein. *Br. J. Pharmac.*, **39**, 465–475.
- Docherty, J. R. & Hyland, L. (1986). An examination of 5-hydroxytryptamine receptors in human saphenous vein. *Br. J. Pharmac.*, **89**, 77–81.
- Horwitz, D., Clineschmidt, B. V., Vanburen, J. M. & Ommaya, A. K. (1974). Temporal arteries from hypertensive and normotensive man. Reactivity to norepinephrine and characteristics of α -adren-
ergic receptors. *Circulation Res.*, **34**, (suppl 1), 109–115.
- Innes, I. R. (1962). An action of 5-hydroxytryptamine on adrenaline receptors. *Br. J. Pharmac.*, **19**, 427–441, 1962.
- Kassay-Farkas, N., & Wyse, D. G. (1986). Prevention of electrochemical oxidation of norepinephrine caused by transmural electrical stimulation. *Blood Vessels*, **23**, 160–164.
- Kenakin, T. P. & Beek, D. (1981). The measurement of antagonist potency and the importance of selective inhibition of agonist uptake processes. *J. Pharmac. exp. Ther.*, **219**, 112–120.
- Matthews, W. D., Jim, K. F., Hieble, J. P. & Demar-
inis, R. M. (1984). Post-synaptic α -adrenoceptors on vascular smooth muscle. *Fed. Proc.*, **43**, 2923–2928.
- Nie, N. H., Hull, C. H., Jenkins, J. G., Steinbrenner, K. & Brent, D. H. (1975). *SPSS. Statistical Package for the Social Sciences*, 2nd Edition. Toronto: McGraw Hill.
- Ruffolo, R. R. JR. (1984). Interactions of agonists with peripheral α -adrenergic receptors. *Fed. Proc.*, **43**, 2910–2916.
- Skarby, T. V. C., Andersson, K. E. & Edvinsson, L. (1983). Pharmacological characterization of post-junctional α -adrenoceptors in isolated feline cerebral and peripheral arteries. *Acta physiol. Scand.*, **117**, 63–73.
- Tallarida, R. J. & Murray, R. B. (1981). *Manual of pharmacologic calculations with computer programs*. New York: Springer-Verlag.
- Toda, N. (1985). Reactivity in human cerebral artery: species variation. *Fed. Proc.*, **44**, 326–330.
- Vanhoutte, P. M., & Shepherd, J. T. (1985). Adren-
ergic pharmacology of human and canine peripheral veins. *Fed. Proc.*, **44**, 337–340.
- Verbeuren, T. J., Lorenz, R. R., Aarhus, L. L., Shepherd, J. T. & Vanhoutte, P. M. (1983). Pre-junctional beta-adrenoceptors in human and canine saphenous veins. *J. Auton. Nerv. Syst.*, **8**, 261–271.
- Westfall, T. C. (1984). Evidence that noradrenergic transmitter release is regulated by presynaptic receptors. *Fed. Proc.*, **43**, 1352–1357.
- Wyse, D. G. (1980). 'Normalization' of active developed force of isolated strips of muscular and elastic arteries of rat for variations in wall thickness. *J. pharmac. Methods*, **4**, 313–326.
- Wyse, D. G. (1981). Isolated human cystic artery: responses to common agonist and antagonist drugs. *Pharmacology*, **22**, 93–100.
- Wyse, D. G. (1984). Relationship of blood pressure to the responsiveness of an isolated human artery to selected agonists and to electrical stimulation. *J. cardiovasc. Pharmac.*, **6**, 1083–1091.

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